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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/889,355    07/08/97    ENGLER    H    16930-000811

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HM12/0727

EXAMINER

WILSON, M

ART UNIT

PAPER NUMBER

1633

DATE MAILED:

07/27/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.

08/889,355

Applicant(s)

ENGLER ET AL.

Examiner

Michael Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 18 May 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 21,22,35,36 and 40-55 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21,22,35,36 and 40-55 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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## **DETAILED ACTION**

### ***Request for Continued Examination***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5-16-01 has been entered.

Applicant's arguments filed 5-16-01, paper number 20, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-20, 23-34, 37-39 and 56-61 have been canceled. Claims 21, 22, 35, 36 and 40-55 are pending and under consideration in the instant application. The effective filing date of the claimed invention remains July 8, 1997.

### ***Claim Rejections - 35 USC § 112***

1. Claims 21, 22, 35, 36 and 40-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification lacks written description for the impurities of BigCHAP. The specification and claims state X1, X2 or X3 may be a cholic acid or deoxycholic acid group.

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However, the specification does not teach how the cholic or deoxycholic acid groups are attached to Formula I or II. In application 09/112,074, the impurities (Fig. III-V) have three carbons between the carboxyl group and the pentose ring of the cholic acid instead of four as in cholic or deoxycholic acid (i.e. the impurities require X1, X2 or X3 is cholic or deoxycholic acid with a deletion of the terminal O<sub>2</sub>H). Addition of the cholic or deoxycholic acid as claimed (with the terminal O<sub>2</sub>H) would result in four carbons between the carboxyl group and the pentose ring of the cholic or deoxycholic acid which is not the structure of the impurities disclosed in 09/112074. The structures of the impurities disclosed in application 09/112074 are not readily apparent in view of Formulas I or II as filed in the instant application because it was not readily apparent that the cholic or deoxycholic acid groups had a deletion of the terminal O<sub>2</sub>H. Therefore, Formulas I and II are not adequate to describe the impurities of BigCHAP. In conclusion, it was not readily apparent that applicants were in possession of the structures of the impurities of BigCHAP at the time of filing.

Furthermore, it appears that some of the claims are directed toward modifications of Impurities I, II or III or impurities that are different than Impurities I, II or III. The specification does not teach isolating any other impurities from BigCHAP or how to modify impurities I, II or III to obtain other compounds. Since the structure that represents Impurities I, II and III cannot be accurately determined at this time, it cannot be determined which claims are equivalent to Impurities I, II and III and which claims are modifications of Impurities I, II and III or impurities other than Impurities I, II or III. Modifications of Impurities I, II and III and impurities other

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than Impurities I, II and III lack written description because the specification does not teach how to isolate such impurities, how to modify Impurities I, II or III or how to use such compounds to deliver DNA.

2. Claims 21, 22, 35, 36 and 40-55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Claims 21, 22, 35, 36 and 40-55 are not enabled because Formula I (claims 21, 22, 35, 36, 40-53) and Formula II (claims 54 and 55) are not the structures of the impurities found in BigCHAP. Example 11 states three impurities (I, II and III) were isolated from BC BigCHAP, but the specification does not teach how the impurities were isolated or the structure of the impurities. The specification and claims state X1, X2 or X3 in Formulas I or II are cholic or deoxycholic acid. However, the specification does not teach how the cholic or deoxycholic acid groups are attached to Formula I or II. In application 09/112,074, applicants disclose the structure of the impurities (Fig. III-V) which have three carbons between the carboxyl group and the pentose ring instead of four in the cholic or deoxycholic acid (i.e. the impurities require X1, X2 or X3 is cholic or deoxycholic acid with a deletion of the terminal O<sub>2</sub>H). Addition of the cholic or deoxycholic acid would result in four carbons between the carboxyl group and the pentose ring of the cholic or deoxycholic acid which is not the structure of the impurities of BigCHAP. The structures of Impurities I, II and III of BigCHAP are not readily apparent in the

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instant application because it was not readily apparent that the cholic or deoxycholic acid groups had a deletion of the terminal  $O_2H$ . Therefore, Formula I (claims 21, 22, 35, 36, 40-53) and Formula II (claims 54 and 55) are not representative of the structures of Impurities I, II or III of BigCHAP. The specification does not enable one of skill in the art at the time the invention was made to isolate or determine the structure of the Impurities I, II or III of BigCHAP.

Furthermore, it appears that some of the claims are directed toward modifications of Impurities I, II or III or impurities that are different than Impurities I, II or III. The specification does not teach isolating any other impurities from BigCHAP or how to modify impurities I, II or III to obtain other compounds. Since the structure that represents Impurities I, II and III cannot be accurately determined at this time, it cannot be determined which claims are equivalent to Impurities I, II and III and which claims are modifications of Impurities I, II and III. Modifications of Impurities are not enabled because the specification does not teach how to make such compounds or how to use such compounds to deliver DNA.

The specification does not enable one of skill to use DNA combined with Formula I as a pharmaceutical composition (claims 21 and 22) or to treat bladder cancer (claims 35, 36 and 40). The specification does not enable one of skill to isolate or determine the structure of the impurities of BigCHAP, and Formula I does not correlate to the impurities of BigCHAP for reasons cited above. Therefore, the specification does not enable using DNA combined with Formula I as a pharmaceutical composition or to treat cancer as claimed.

In addition, the state of the art at the time of filing was such that it was unpredictable what

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combination of vector, promoter, route of administration, dosage, protein of interest, level of expression, and target tissue were required to obtain a desired therapeutic effect (Eck, Verma, Ross and Marshall all of record). The specification discloses administering adenoviral vector encoding RB operatively linked to a promoter combined with BC BigCHAP to mice and obtaining RB expression (example 6; Fig. 9). The specification does not teach administering  $1 \times 10^8$  to  $5 \times 10^{11}$  particles/ml of an adenovirus (claims 35 and 36) comprising DNA encoding RB provides a therapeutic effect. The specification does not teach the level of RB expression obtained, the level of RB expression required to obtain a therapeutic effect or that administration of the adenoviral vector and BC BigCHAP resulted in a therapeutic effect.

The specification does not provide adequate guidance for one of skill to determine the vector, promoter, route of administration, dosage, protein of interest, level of expression, and target tissue required to obtain a therapeutic effect using RB or any other therapeutic DNA. Given the unpredictability in the art regarding how to obtain a therapeutic effect using DNA taken with the guidance provided in the specification, applicants have not provided one of skill with adequate guidance for how to use DNA combined with Formula I as a pharmaceutical composition (claims 21 and 22) or to treat bladder cancer (claims 35, 36 and 40).

Claims 35, 36 and 40 are not enabled because they are missing essential elements. The claims are directed toward treating bladder cancer using a therapeutic agent formulated in Formula I. The claims are not limited to a therapeutic agent that is a vector encoding a therapeutic protein operatively linked to a promoter which is considered essential to the invention.

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Nor do the claims recite the protein of interest, require administering the cell or the composition to an individual with bladder cancer, expression of the therapeutic protein to therapeutic levels or treating bladder cancer which are also essential to the invention based on the unpredictability in the art.

Applicants argue Example 12 discloses how to synthesize the compounds of Formula I. Applicants argument is not persuasive. Example 12 does not disclose isolating Formula I or the structure of Formula I. Applicants argue Example 11 discloses how to isolate Formula I from BigCHAP. Example 11 states Formula I was isolated from BigCHAP but does not teach how Formula I was isolated from BigCHAP or the structure of Formula I. Applicants argue Example 11 teaches how to use the compounds of the invention. Applicants argument is not persuasive because the impurities do not have the structure of Formulas I or II, because the specification does not teach how to isolate the impurities of BigCHAP or the structure of the impurities of BigCHAP.

3. Claims 21, 22, 35, 36 and 40-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 22, 35, 36 and 40-55 are indefinite because the structure of the impurities of BigCHAP recited in the claims is unclear. Example 11 states three impurities (I, II and III) were isolated from BC BigCHAP, but the specification does not teach how the impurities were isolated or the structure of the impurities. The claims state X1, X2 or X3 in Formulas I or II are cholic or



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deoxycholic acid. However, the specification does not teach how the cholic or deoxycholic acid groups are attached to Formula I or II. In application 09/112,074, applicants disclose the structure of the impurities (Fig. III-V) which have three carbons between the carboxyl group and the pentose ring instead of four in the cholic or deoxycholic acid (i.e. the impurities require X1, X2 or X3 is cholic or deoxycholic acid with a deletion of the terminal O<sub>2</sub>H). Addition of the cholic or deoxycholic acid would result in four carbons between the carboxyl group and the pentose ring of the cholic or deoxycholic acid which is not the structure of the impurities of BigCHAP. Therefore, the structures of the compounds recited in the claims are indefinite because they are not the structures of the impurities of BigCHAP disclosed in 09/112074.

Claims 21, 22, 35, 36 and 40 are indefinite because they are dependent upon claims which have been canceled. Incorporation of the canceled subject matter into the claims is required.

Claim 40 is indefinite because "the delivery enhancing agent" lacks antecedent basis.

#### ***Claim Rejections - 35 USC § 102***

4. Claims 41, 42, 45, 54 and 55 remain rejected and claims 43, 44 and 46-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Aungst (1993, Int. J. Pharm., Vol. 53, pages 227-235) for reasons of record.

Aungst taught BC BigCHAP (page 230, Figure 1; page 228, column 2, line 17 of Materials). BigCHAP is equivalent to the structure in claims 41, 42, 45 and 54. As drawn on page 5 of applicants response, the ring structure attached to the carboxyl group on the left is

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equivalent to X1 and the two groups attached to the two carboxyl group on the right are equivalent to X2 and X3 which is equivalent to claims 41, 42, 45 and 55. In addition, BC BigCHAP inherently contains the Impurities I, II and III disclosed in the instant invention and the compounds in claims 43, 44 and 46-53.

Applicants argue the claims exclude BC BigCHAP and are limited to Impurities I, II and III isolated from BC BigCHAP. Applicants argument is not persuasive. The structure of BigCHAP is the same as claims 41, 42, 45 and 54. In addition, the claims use open language are not limited to Impurities I, II or III and BC BigCHAP inherently has the impurities I, II and III. Therefore, BC BigCHAP containing Impurities I, II and III anticipates the claims.

Applicants argue that a compound that is purer than a previously known compound is patentable. While that is true applicants argument is not persuasive. The claims are not limited to Impurities found in BigCHAP. The structure of BigCHAP is the same as claims 41, 42, 45 and 54. In addition, Formulas I and II do not accurately reflect the structures of Impurities I, II or III (see 112/written description, enablement, and indefiniteness rejections above). Therefore, the compounds recited in the claims are not limited to the purer compounds found in BigCHAP.

Applicants argue the structure of BigCHAP differs from the structure claimed. Applicants argument is not persuasive. As drawn on page 5 of applicants response, the ring structure attached to the carboxyl group on the left is equivalent to X1 and the two groups attached to the two carboxyl group on the right are equivalent to X2 and X3 which is equivalent to claims 41, 42, 45 and 55.

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*Claim Rejections - 35 USC § 103*

5. Claims 40 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson (U.S. Patent, 5,804,566, Sept. 8, 1998) for reasons of record.

Aungst taught administering compounds to rats using BC BigCHAP (page 230, Figure 1; page 228, column 2, line 17 of Materials). BC BigCHAP inherently contains the Impurities I, II and III disclosed in the instant invention. As drawn on page 5 of applicants response, the ring structure of BigCHAP attached to the carboxyl group on the left is equivalent to X1 and the two groups attached to the two carboxyl group on the right are equivalent to X2 and X3 which is equivalent to claims 41, 42, 45 and 55. BigCHAP is a "delivery enhancing agent" as in claim 40. Aungst did not teach delivering DNA using BC BigCHAP. However, Carson taught delivering DNA using surfactants and absorption promoters (column 8, lines 55-63). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer compounds to rats using BC BigCHAP as taught by Aungst wherein the compound was DNA as taught by Carson. One of ordinary skill in the art at the time the invention was made would have recognized that BigCHAP was a surfactant and would have been motivated to add BigCHAP to DNA to improve delivery of a compound to a cell as taught by Aungst (page 230, Table 1).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

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suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art at the time the invention was made would have recognized that BigCHAP was a surfactant and would have been motivated to use BigCHAP as the surfactant to deliver DNA to improve delivery of a compound to a cell as taught by Aungst (page 229, col. 2, "Results;" page 230, Table 1). Applicants claims are not limited to delivery of the impurity and DNA; therefore, the cited references provide adequate guidance to deliver DNA with CB BigCHAP.

Claims 21 and 22 appear to be free of the prior art of record because the prior art of record did not teach or suggest combining DNA, the compound of Formula I and polymeric matrix or mucoadhesive. Claims 35 and 36 appear to be free of the prior art of record because the prior art of record did not teach or suggest administering  $1 \times 10^8$  to  $5 \times 10^{11}$  particles/ml of an adenovirus comprising a therapeutic gene formulated in a buffer comprising the compound of Formula I.

### ***Conclusion***

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner

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should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

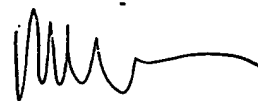
Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



**MICHAEL C. WILSON**  
**PATENT EXAMINER**